# *ABC of allergies*
# Pathogenic mechanisms: a rational basis for treatment

Peter H Howarth

Allergic diseases such as asthma, rhinitis, eczema, and anaphylaxis are increasingly common and, in addition to being associated with morbidity and potential mortality, constitute a considerable burden on health resources, with both direct and indirect costs. This article discusses the pathogenic mechanism underlying the clinical signs and symptoms of these diseases and explains the basis for the choice of differing treatments.

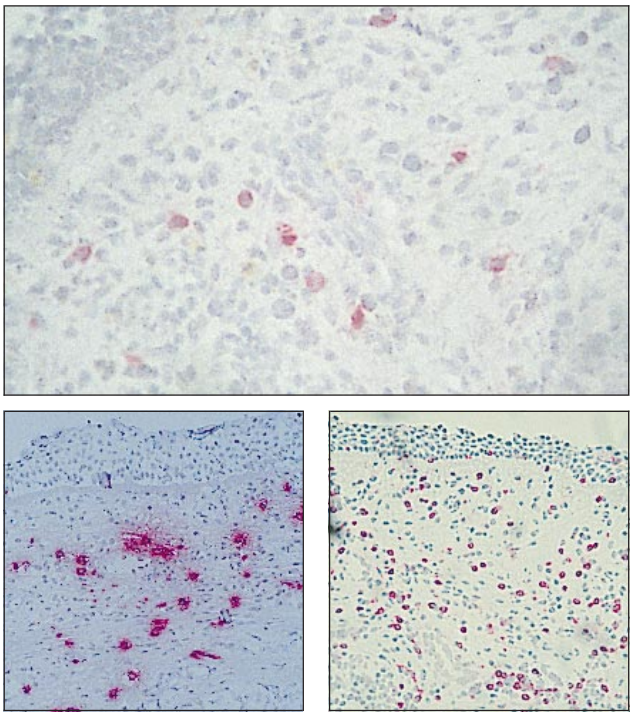
## Relation of atopy and allergy to disease

About 40% of the population is atopic as evidenced by a positive response to a skin prick test with an allergen, but not all show signs and symptoms of clinical disease. There may be a latency period, as students who have positive skin prick tests with grass pollen but who do not experience hay fever have been shown to go on to develop seasonal allergic rhinitis. A threshold response may also be required for signs and symptoms of clinical disease to develop, as allergic airway inflammation is present in the lower airways of patients with perennial allergic rhinitis sensitive to house dust mite who do not have clinical asthma. This inflammatory response falls between the response in patients with clinical asthma and that in non-atopic healthy controls.

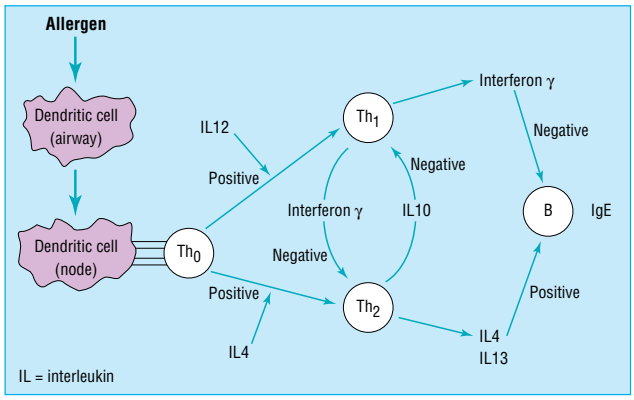
The situation is, however, more complex than this, as patients with comparable responses to skin prick testing may have solely asthma, rhinitis, or eczema, and current research to explain organ-specific disease is focusing on the local tissue production of IgE and on the role of selective homing and activation of T lymphocytes, which may amplify the local tissue response. It is, however, possible in sensitised individuals to link allergen exposure to signs and symptoms of clinical disease, as seasonal exposure to aeroallergens (such as tree or grass pollens or fungal spores) induces seasonal allergic rhinoconjunctivitis, and exposure to perennial allergens (usually indoor allergens such as house dust mite or other animal allergens) is associated with persistent signs and symptoms of disease (asthma or rhinitis, or both). Intermittent exposure to systemic allergens, such as food, drugs, or venom, can induce acute disease (anaphylaxis, urticaria, dermatitis, asthma, rhinitis), which may take a variable time to resolve. IgE mediated reactions underlie these clinical responses.

## Immunoglobulin E

An increase in specific IgE is reflected by positive skin prick tests to allergens or by positive in vitro tests such as the radioallergosorbent test. Specific IgE is generated by B lymphocytes under the regulation of cytokines generated by T lymphocytes. Cytokines are small molecular weight chemicals that have a localised action in modulating cell function. The cytokines that favour IgE isotype switching (interleukin 4 and interleukin 13) are generated by a subpopulation of T lymphocytes with a T helper 2 cytokine profile, whereas T cells that generate a T helper 1 cytokine profile—by secreting interferon gamma—inhibit B cell isotype switching for IgE synthesis. Th1 and Th2 cells reciprocally inhibit each other's development. In atopy the production of IgE is increased,



Immunohistology of nasal mucosa in allergic rhinitis using alkaline phosphatase/anti-alkaline phosphatase technique showing individual cells stained red: mast cells (top), eosinophils (bottom left), and CD4 T lymphocytes (bottom right)




Regulation of B lymphocyte IgE synthesis by T lymphocytes. T cells with the Th2 cytokine profile increase interleukin 4 and interleukin 13 synthesis, which promotes IgE isotype switching, whereas the development of T cells with a Th1 cytokine profile, which generate the interferon gamma, inhibits B cell isotype switching for IgE synthesis. This process also involves antigen uptake and processing by mucosal dendritic cells (commonly Langerhans' cells in the airways) and the presentation of antigen in a modified format to T lymphocytes, typically in a draining lymph node

suggesting an imbalance in the ratio of Th2 to Th1 control. The development of Th2 secreting lymphocytes requires interleukin 4. This cytokine is generated by the placenta to prevent immunological fetal rejection (a Th1 cytokine response). It has been proposed that that persistence of this placental Th2 drive—possibly related to improved or altered nutrition in the absence of a Th1 counter switch—is the major factor contributing to the increasing prevalence of allergic disease in the past 30-40 years. An additional contributory factor may be a decrease in severe infection in early infancy over the same period and an interaction between allergens and atmospheric pollution that potentiates the tendency to sensitisation. Infection would drive a Th1 response and thus down regulate the tendency for Th2 related disease to develop.

**Airways inflammation underlies clinical disease expression in allergic asthma and rhinitis**

## Mediators of hypersensitivity

IgE binds to tissue mast cells and circulating basophils through cell-surface expressed high affinity receptors. Allergen binds to specific IgE and induces cell activation, with the tissue release and generation of mediators such as histamine, tryptase, leukotrienes, prostaglandins, and kinins from mast cells contributing to symptoms of asthma and rhinitis through direct actions on neural and vascular receptors and within the lower airways also on airway smooth muscle receptors.

Histamine and leukotriene release from basophils, as well as mediator release from mast cells, will contribute to circulatory events in anaphylaxis. The release of these mediators is rapid (minutes) and produces immediate symptoms. In the upper airways this is associated with nasal itch, sneeze, and rhinorrhoea (which are all neurally mediated), as well as with nasal obstruction (which is vascular in origin). In the lower airways mediator release is associated with bronchoconstriction and hypersecretion of mucus, giving rise to tightness in the chest, breathlessness, cough, and wheeze. The stimulation of sensory nerves with neuropeptide release (substance P and calcitonin gene related peptide) may enhance the response. During persistent exposure to an allergen, as occurs in seasonal and perennial allergic rhinitis and allergic asthma, there is also tissue accumulation of eosinophils. Activation of eosinophils with leukotriene release contributes to signs and symptoms of clinical disease, as does mediator release from activated epithelial cells.

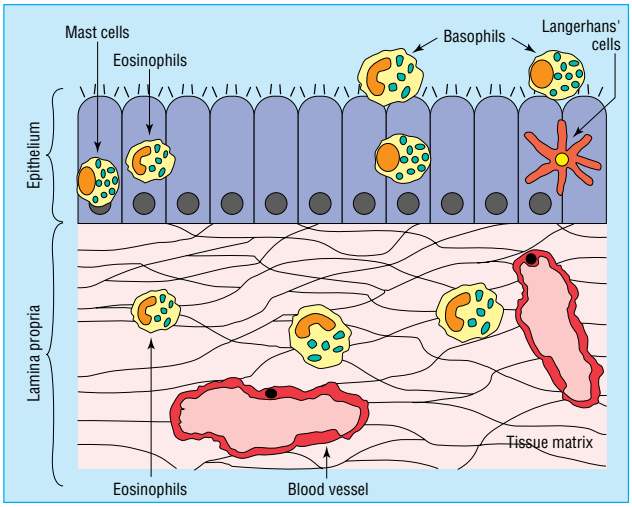
**Contribution of mediators to signs and symptoms of disease**

| | Signs and symptoms | |
|---|---|---|
| **Mediator** | **Rhinitis** | **Asthma** |
| *Histamine* | Itch; sneeze; rhinorrhoea; obstruction | Bronchoconstriction; plasma protein exudation; mucus secretion |
| *Leukotrienes* | Possible rhinorrhoea; obstruction | Bronchoconstriction; plasma protein exudation; mucus secretion |
| *Kinins* | Obstruction | Bronchoconstriction; cough |
| *Prostaglandins* | Obstruction | Bronchoconstriction (prostaglandin $E_2\alpha$, prostaglandin $D_2$); anti-bronchoconstrictor (prostaglandin $E_2$); cough (prostaglandin $F_2\alpha$) |
| *Endothelin* | Itch; sneeze; rhinorrhoea | Bronchoconstriction |

## Inflammatory accumulation and cell activation

Biopsy studies in asthma, rhinitis, and conjunctivitis specifically show an accumulation of effector cells in the epithelium, with an increase of mast cells, eosinophils, and basophils. The accumulation of inflammatory cells in the epithelium in patients with hay fever during the grass pollen season underlies the clinical observation of "priming," a situation in which patients' symptoms are more severe later in the season than at the start, despite the same pollen concentration. Eosinophil accumulation, along with an increase in T lymphocytes, is evident in the dermis in atopic dermatitis (eczema).

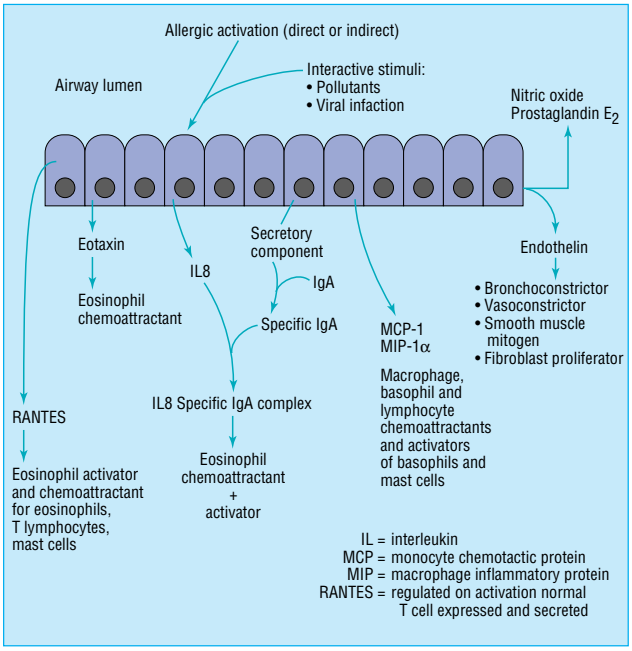
The local release of cytokines and chemokines (chemotactic cytokines) from activated T lymphocytes, mast cells, and epithelial cells can account for this accumulation of inflammatory cells in the airways. For T cell activation there has to be a specific interaction between the T cell and an antigen presenting cell, which processes the allergen and presents it to the T cell in a modified format. The major antigen presenting cells in the airways and skin are dendritic or Langerhans' cells,



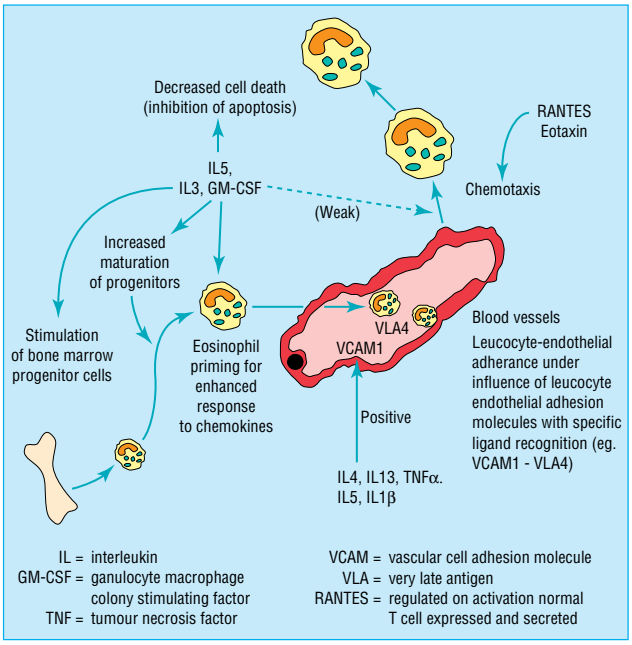

Changes in the number of cells in allergic airways disease: an accumulation in the epithelium of the major effector cells of the allergic reaction (mast cells, eosinophils, and basophils) and antigen presenting cells (Langerhans' cells); and an increase in eosinophils in the submucosa and in a subpopulation of fibroblasts ("myofibroblasts") in the tissue matrix (not illustrated)

and these are found to accumulate in the airway epithelium and have been reported to express high affinity IgE receptors. There is evidence in perennial asthma, perennial rhinitis, and acute atopic dermatitis for an increase in T cells exhibiting a Th2 cytokine profile.

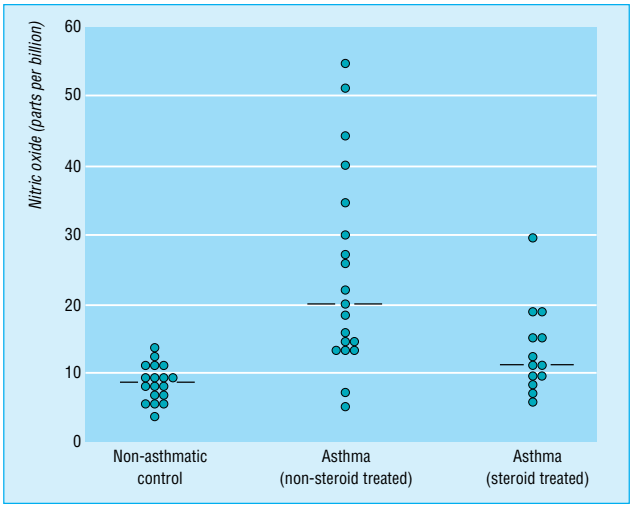
Th2 cytokines act in concert to promote an accumulation of eosinophils in the airways through endothelial activation and the enhanced adherence of these leucocytes to the vascular endothelium. They do this by increasing the eosinophil chemotactic response to chemokines, stimulating marrow generation of progenitor cells, and decreasing tissue removal by inhibiting apoptosis (cell death). The directed movement of these cells, and of mast cells, basophils, T lymphocytes, and Langerhans' cells, is regulated by chemokine release from activated epithelial cells. Epithelial cells represent the primary mucosal interface with the environment, and the activation of epithelial cells by other environmental factors, such as pollutants or viral infection, provides a basis for their interaction in allergic airways disease. This epithelial activation in allergic airways disease is indirectly reflected by raised concentrations of nitric oxide in exhaled air, as the inducible form of an enzyme, nitric oxide synthase, is up regulated and may provide a potentially measurable marker to monitor the impact of anti-inflammatory treatment.




Epithelial activation and airway inflammation: products generated by epithelial cells in allergic airways disease and their relation to inflammatory cell recruitment




Processes involved in recruitment and retention of eosinophils in the airways. Cytokines (predominantly interleukin 5) stimulate bone marrow progenitor cells, cell priming, and adherence of leucocytes to the endothelium. Cytokines stimulate the endothelial cells, with specific leucocyte endothelial cell adhesion molecule expression and binding to cell-surface expressed ligands. Chemokines influence cell chemotaxis




Measurement of nitric oxide in oral exhaled air in mixed expired air sample in non-asthmatic healthy controls (n=18), asthmatic patients not treated with steroids (n=19), and asthmatic patients receiving inhaled steroid treatment (n=13). Horizontal lines indicate median values for each group

## Implications for treatment

### Allergen avoidance

The first step in management once allergy has been diagnosed is allergen avoidance. Allergen avoidance can help to reduce disease severity and minimise treatment in patients with asthma, rhinitis, and atopic dermatitis. The essential principle is thus to identify the provoking allergens and where possible ensure that the patient avoids them. Identification is based on clinical history and on objective assessment of the presence of specific IgE. Avoidance protocols will be discussed in a later article.

**Allergen avoidance can be life saving in patients with anaphylaxis**

## Pharmacotherapy

Adrenaline is first line treatment for anaphylaxis and is most effective when administered early. Glucocorticoids represent the most efficacious treatment when administered as regular prophylactics. They regulate gene transcription and down regulate cytokine and chemokine synthesis, thus indirectly inhibiting cell recruitment and cell activation. Glucocorticoid treatment reduces epithelial and endothelial cell activation; reduces accumulation of epithelial mast cells, eosinophils, and Langerhans' cells; enhances eosinophil apoptosis; and reduces T cell and mast cell cytokine generation. The treatment is best administered topically to the airways and skin to reduce the possibility of systemic side effects.

Cromones are less effective as anti-inflammatory agents as they have a more restricted profile of effects. Specific end organ receptor antagonists ($H_1$ antihistamines, anticholinergic agents, and leukotriene receptor antagonists) and functional antagonists (β adrenoceptor agonists (bronchodilators) and α agonists (vasoconstrictor decongestants)) will be limited by their specificity of action, although the oral treatments have value in targeting upper and lower airways as well as the conjunctiva.

Histamine is a dominant mediator in the upper airways ($H_1$ receptor mediated), and leukotrienes are a significant contributor to lower airways disease (leukotriene $C_4$ and $D_4$ receptor mediated).

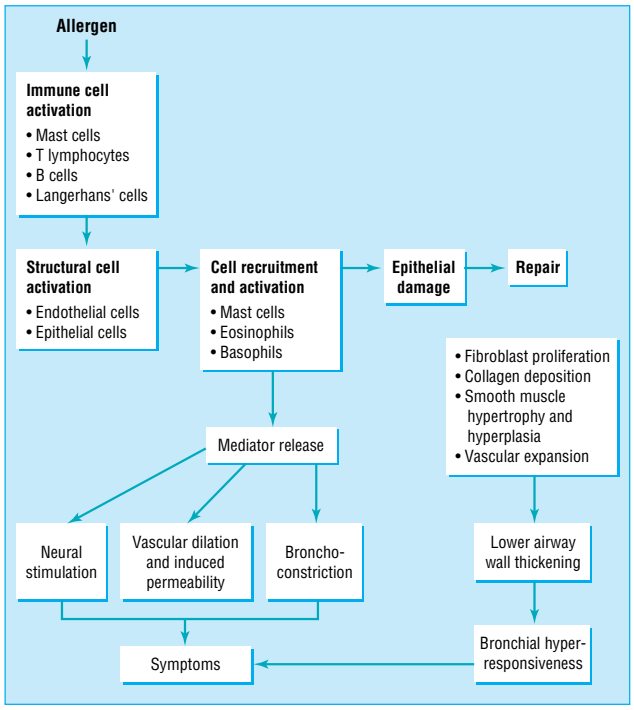
The importance in asthma of targeting the airway inflammation rather than the end organ effects is emphasised by the British guidelines on asthma management as this approach not only leads to improved disease control but also can prevent irreversible loss of lung function if used early in disease management. This loss of lung function is attributable to chronic structural airway changes that develop if allergic inflammation is left untreated.

## Immunotherapy

Allergen immunotherapy is the repeated administration of low doses of an allergen to which an individual is sensitised in a stepwise incremental pattern, usually by subcutaneous injection, over some years (usually three to five). This is done to influence the state of immunological and clinical tolerance. This treatment is thought to act via either immune deviation of T lymphocyte responses from a Th2 to a Th1 profile or by the induction of T cell unresponsiveness (anergy). Although immunotherapy is well established for seasonal allergic rhinitis, it is a less well proved approach for house dust mite sensitive asthma and rhinitis. It is the primary treatment to consider for modifying sensitisation to bee and wasp venom.

## Future approaches

Treatments are being developed that focus on inhibiting the interaction between IgE and allergen; inhibiting cytokine or chemokine function (such as a monoclonal antibody to interleukin 5 or a chemokine receptor antagonist); inhibiting T cell activation; modifying endothelial leucocyte interactions (very late antigen 4 antagonist); and modifying epithelial cell activation. The long term future must, however, depend on a better understanding of the basis for the increase in allergic diseases so that they can be prevented, rather than depending on secondary disease control.




Progression of the allergic process in the airways and the relation of this process to inflammatory cell recruitment and symptom expression

## Further reading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Mikila Jacobson and Stephen Durham provided the histology photographs.

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The ABC of allergies is edited by Stephen Durham, honorary consultant physician in respiratory medicine at the Royal Brompton Hospital, London. It will be published as a book later in the year.

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